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Therapeutic Class Review
Dopamine Precursor/Dopa Decarboxylase Inhibitors

Overview/Summary

Parkinson's disease is characterized by a lack of dopamine in the corpus striatum region of the brain. Levodopa is the chemical precursor to dopamine and effectively crosses the blood-brain barrier where it is converted to dopamine and causes improvement of Parkinson's symptoms. When administered orally levodopa is rapidly converted to dopamine in the extracerebral tissue and only a small portion of active dopamine is transported to the brain. Carbidopa inhibits the conversion of levodopa to dopamine in the peripheral tissues allowing more levodopa to be transferred to the brain. The coadministration of levodopa and carbidopa effectively increases the half-life of levodopa from 50 minutes to 1.7 hours and allows for the use of smaller amounts of levodopa doses to produce the desired effect on the patient symptoms.[1-6]

Carbidopa/levodopa is available generically as well as the branded agents Sinemet® and Sinemet-CR® and Parcopa®.[2-6]

The National Institute for Health and Clinical Excellence (NICE) guidelines state that there are no universal first-choice agents for patients with early or late Parkinson's disease. They recommend that levodopa can be used in patients with early Parkinson's disease; however the dose should be kept as low as possible in order to minimize the development of motor complications.[7]

The American Academy of Neurology guidelines state that levodopa is the most effective of all drugs for symptoms of Parkinson's disease. The guidelines also discuss that clinical trials have shown that early use of levodopa therapy might predispose patients to develop long-term motor complications such as wearing-off and dyskinesia. Their recommendation is that patients who require symptomatic treatment can be started on anticholinergic therapy or selegiline prior to the administration of dopaminergic treatment. When selecting the appropriate dopaminergic treatment either levodopa or dopamine agonists are appropriate. However the treatment choice is dependent on the impact of improving motor disability which is better improved by levodopa, and the lessening of motor complications which is better with dopamine agonists.[8-9]

The European Federation of Neurological Societies guidelines state that levodopa is the most effective symptomatic antiparkinsonian drug available. The guidelines for early Parkinson's disease recommend that for younger patients with Parkinson's disease a dopamine agonist should be initiated first, in order to prolong the use of levodopa and delay the development of motor complications. For the elderly, early use of levodopa is recommended as this patient population is less prone to developing motor complications.[10-11]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Carbidopa/levodopa (Sinemet®, Sinemet-CR®, Parcopa®)	*Dopamine Precursor/Dopa Decarboxylase Inhibitors*	✔

Indications

Table 2. Food and Drug Administration Approved Indications[2-6]

Generic Name	Idiopathic Parkinson's Disease	Postencephalitic Parkinsonism	Symptomatic Parkinsonism
Carbidopa/levodopa	✔	✔	✔

In addition to its Food and Drug Administration approved indications, carbidopa/levodopa may also be used off-label for restless leg syndrome.[6]

Pharmacokinetics

Table 3. Pharmacokinetics[2-6]

Generic Name	Bioavailability (%)	Metabolism	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Carbidopa/ levodopa	80-99; 70-75 (controlled release)	Levodopa: liver, gut, kidney Carbidopa: liver	Levodopa: Urine: 70-80 Carbidopa: Urine: 30	Dopamine, 3-O-Methyldopa	Levodopa: 1.7 hours Carbidopa: 1.6-2 hours

Clinical Trials

Carbidopa/levodopa has been used in clinical practice for many years, and studies have shown that the various dosage formulations are efficacious when compared to placebo. This combination product has also been shown to be one of the more efficacious agents in the treatment of Parkinson's disease. There have been a vast number of clinical trials conducted evaluating the efficacy and safety of carbidopa/ levodopa. However the majority of literature supporting the use of this agent was either published decades ago or are lacking in statistical significance and detail. The following studies have been identified to best portray the safety and efficacy of this combination product.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Macleod et al[1] Selegiline or rasagiline or lazabemide vs placebo, levodopa or dopamine agonist	MA Randomized clinical trials comparing MAO-B inhibitors with a control intervention in early Parkinson's disease, studies included recruited patients with a clinical diagnosis of idiopathic Parkinson's disease who have not started treatment or had started treatment within 12 months and had a Hoehn and Yahr Stage-II or less	N=2,422 (10 studies) 1 to 9.2 years Mean duration=5.8 years	Primary: Effectiveness evaluated by: number of patients who were either dead or disabled from any cause at end of follow-up, the number of deaths that occurred, disease progression in terms of severity of impairment, disability and quality of life which were measured by scales (UPDRS and UPDRS ADL), levodopa requirement, mean levodopa dose, the number of patients requiring levodopa, time to the introduction of levodopa or a dopamine agonist, number of patients with motor fluctuations, number of patients with dyskinesias, safety (number of patients with	Primary: All the studies were evaluated, they all reported data on death at the end of follow-up. Data was available for 2,389 patients (98.7% of all patients). Overall there was a non-significant increase in deaths amongst patients treated with MAO-B inhibitors compared with those given control (OR, 1.16; 95% CI, 0.92 to 1.44; *P*=0.21). UPDRS motor scores at one year follow up were reported from two studies (217 patients, 9% of all patients), in which both studies favored treatment with MAO-B inhibitors (*P* value not reported). Mean change in UPDRS-ADL score from baseline to endpoint were reported from six studies (1,262 patients, 52% of all patients, 88% randomized in the six studies), and favored treatment with MAO-B inhibitors (95% CI, -2.53 to -0.48; *P*=0.004). Participants requiring levodopa were reported from three studies (1,088 patients, 77% without levodopa at the beginning), and favored treatment with MAO-B inhibitors (OR, 0.53; 95% CI, 0.36 to 0.79; *P*=0.01). The absolute rate of requiring levodopa at one year varied in the control groupZ of the three trials from 15% to 60%. Time until levodopa was required was reported from five studies (1,288 patients, 91% of patients in trials without levodopa from the outset), however the data from these studies was skewed and it was not possible to use formal meta-analysis. However, the data from these studies showed a delay in the median time to introduce levodopa with MAO-B inhibitor treatment between 4.1 and 8.7 months. Mean levodopa dose data was reported from five clinical trials. Meta-analysis could not be conducted because the data was skewed with substantial heterogeneity. All the studies showed higher levodopa doses in the control groups compared to the patients treated with MAO-B inhibitors. The difference in levodopa dose varied from 30 to 185 mg/day and generally increased as the duration of follow-up increased. Motor fluctuations data was reported from five clinical trials (1,319 patients, 54% of all patients, 80% of those randomized in the five clinical trials). Delaying the

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			adverse events, number of withdrawals due to adverse events and total number of withdrawals) Secondary: Not reported	development of motor complications significantly favored the MAO-B inhibitors. (OR, 0.75; 95% CI, 0.59 to 0.94; *P*=0.01). In addition, there was no difference between the high-quality trials and the low quality trials (*P*=0.78) and there was no difference between the trials that used levodopa at the beginning and the trials that used MAO-B inhibitors alone from onset (*P*=0.29). Dyskinesia data was reported from four studies (1,228 patients, 51% of all patients, 80% of those randomized in the four trials). The results demonstrated no difference between the intervention group and the control group. Four clinical trials (614 patients, 26% of all patients, 97% of those randomized in the four clinical trials) reported the number of patients with any serious adverse event. Overall, there was a non-significant trend for more adverse events with the MAO-B inhibitors (OR, 1.38; 95% CI, 0.92 to 2.06; *P*=0.12). In five studies (1,203 patients, 50% of all patients), patients treated with MAO-B inhibitors reported the occurrence of nausea more than patients treated with the control. However, the overall difference compared to the control group was non-significant (*P* value not reported). Six trials (1,226 patients, 51% of all patients) reported the number of withdrawals due to an adverse event at the end of follow-up. There were significantly more withdrawals with the MAO-B inhibitors compared to the control group (OR, 2.36; 95% CI, 1.32 to 4.20; *P*=0.004). The rate of withdrawal in the control group was about 10% implying that every ten patients treated there would be one expected withdrawal for a patient treated with an MAO-B inhibitor. There were no significant differences between high and low quality studies (*P*=0.47) and trials that initiated levodopa or dopamine agonist from the beginning (*P* value not reported) and trials which initiated MAO-B inhibitors alone from the outset (*P*=0.70). The total number of withdrawals was not reported.

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van Hilten et al[12] bromocriptine vs levodopa or bromocriptine/ levodopa vs levodopa	MA All randomized controlled trials comparing bromocriptine with levodopa in early Parkinson's disease who had never used bromocriptine and patients who have used levodopa for only a short period (<6 months)	N=850 (6 studies) 11.6 to 25.0 months	Primary: Motor complications, symptomatic efficacy and occurrence of side effects and dropouts Secondary: Not reported	Primary: Dyskinesias were reported in all six trials. In two trials (<18 months) dyskinesias did not occur or occurred in one participant in both groups. Re-analysis of three longer trials indicate a lower occurrence of dyskinesia in the bromocriptine group, however, statistical significance in the largest trial was only demonstrated after three years of treatment (*P* value not reported). Dystonia was reported in five clinical trials. In four studies, dystonia was reported less frequently in the bromocriptine group and was only statistically significant in one trial (*P* value not reported). Wearing-off was reported in two clinical trials. In one study wearing-off occurred in three patients on bromocriptine (N=21) and one participant on levodopa after two years (N=61). However, at four and five years wearing-off was found significantly more often in the levodopa group (*P* value not reported). On-off was reported in three clinical trials. After three years in one of the trials, a statistically significant number of participants with on-off fluctuations occurred in patients using levodopa (*P* value not reported). On-off fluctuations were reported in one participant after five years in one other study. Severity of motor complications was reported in two clinical trials. In one study using the UPDRS-scale item on dyskinesia, severity of dyskinesia was reported to be mild with no major difference between the treatment groups. In the same study, wearing-off was graded as mild in both treatment groups as well. In another study, a 0 to 4 scale was used to score the severity of motor complications in which no difference between groups were observed. Impairment was reported in six clinical trials. One study, reported the sum score of the Webster rating scale, and demonstrated statistical significance favoring levodopa monotherapy during the first year of follow-up. Comparisons at three years were not reported. In two other studies, the Columbia Rating Scale was used, which demonstrated no significant difference in the mean change from baseline between both study groups. Other studies found no difference between study groups at final assessment.

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				Disability was reported in four studies. In three studies, there was no significant difference between groups with respect to change from baseline. In one other study, no formal results were reported but clinicians mentioned a similar trend was demonstrated with the Webster Rating Scale. In one study, nausea occurred in 12 participants on levodopa (N=24) and seven participants on bromocriptine (N=23). One study reported that one participant in each study group experienced hallucination. Another study reported that nausea and hallucinations were reported by more patients on levodopa. Three other studies reported side effects that resulted in withdrawals. In terms of withdrawals, one study reported one participant on bromocriptine stopped therapy because of loss of efficacy and one participant on levodopa dropped out because of elevated liver enzymes. Another study reported three dropouts, one participant in each study group because of nausea, and one in the bromocriptine group due to an allergic reaction. During a dose-titration phase in one study, bromocriptine treated patients dropped out because of nausea (N=3) and confusion (N=1) while there were no withdrawals in the levodopa group. Secondary: Not reported
Marek et al[13] Pramipexole 0.5 mg TID increased as needed to maximum of 4.5 mg daily vs carbidopa/levodopa 25/100 mg TID increased as needed to a maximum of 150/600 mg daily	DB, MC, PG, R Patients with early Parkinson's disease requiring dopaminergic therapy	N=82 4 years	Primary: The mean change from baseline in striatal [^{123}I]β-CIT uptake (a useful marker of disease progression) after 46 months Secondary: The percentage and absolute changes from baseline in striatal, putamen, and	Primary: Pramipexole treatment was associated with a slower rate of decline from baseline in striatal [^{123}I]β-CIT uptake with a mean change from baseline of -16.0% (13.3%) compared to -25.5% (14.1%) in the levodopa group (*P*=0.01). Secondary: Pramipexole also demonstrated less of a decline in striatal [^{123}I]β-CIT uptake compared to levodopa at months 22 (-7.1% [9.0] vs -13.5% [9.6]; *P*=0.004) and 34 (-10.9% [11.8] vs -19.6% [12.4]); *P*=0.009). Results were similar for putamen [^{123}I]β-CIT uptake after 22 months (-7.9% [13.7] for pramipexole vs -16.9% [12.9] for levodopa; *P*=0.005) and 34 months (-11.4% [15.3] for pramipexole vs -24.2% [15.5] for levodopa; *P*=0.001), as well as caudate [^{123}I]β-CIT uptake after 22 months (-6.4% [8.8] for pramipexole vs -11.8% [9.4] for levodopa; *P*=0.02) and 34 months (-10.3% [11.7] for pramipexole vs -17.2% [12.4]

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Supplemental levodopa was prescribed as needed.			caudate ^{123}I] β-CIT uptake (a useful marker of disease progression) after 22 and 34 months, clinical severity of Parkinson's disease using the UPDRS 12 hours off medication	for levodopa; *P*=0.04). A significant decrease in both the mean total and motor UPDRS scores from baseline was observed in the levodopa group (-3.3 vs 0.9 in the pramipexole group and -2.5 vs 0.0 in the pramipexole group respectively) at month 22. Differences between groups in UPDRS scores did not reach statistical significance at months 34 or 46.
Inzelberg et al[14] Pramipexole vs ropinirole vs cabergoline vs levodopa	SR Patients with early Parkinson's disease	N=981 (3 trials) 2-5 years	Primary: Proportion of patients who developed dyskinesia, patient withdrawals, change from baseline in scores for motor function and activities of daily living, adverse events Secondary: Not reported	Primary: Fewer patients developed dyskinesia with dopamine agonist use than with levodopa treatment (*P*<0.01 for all three). The decrease in risk was similar among groups with an OR of 0.25 (95% CI, 0.13 to 0.47) for pramipexole, 0.31 (95% CI, 0.18 to 0.53) for ropinirole and 0.38 (95% CI, 0.19 to 0.78) for cabergoline all compared to levodopa. Differences in the incidence of withdrawals relative to levodopa did not reach statistical significance for ropinirole (OR, 1.13; 95% CI, 0.68 to 1.88), pramipexole (OR, 1.24; 95% CI, 0.64 to 2.39) or cabergoline (OR, 1.24; 95% CI, 0.71 to 2.14). Improvements in motor function were found to be greater in the levodopa treatment arm than both pramipexole (*P*=0.001) and ropinirole (*P*=0.008). The adjusted mean changes in the motor scores were reported as 3.90 for pramipexole and 4.48 for ropinirole with a difference of 0.58 (95% CI, -4.20 to 3.13; *P*=0.759), thus the difference between each dopamine agonist compared to levodopa was comparable. Levodopa also demonstrated a significantly greater benefit in ADL's over pramipexole (*P*<0.001), but not ropinirole (*P*=0.08). The adjusted mean changes in the ADL scores were reported as 5.000 for pramipexole and 1.530 for ropinirole with a difference of 3.470 (95% CI, 0.363 to 6.580; *P*=0.029). Results of these two outcomes were not reported for cabergoline. The incidence of edema was reported more often in the dopamine agonist arms as opposed levodopa. Odds ratios were reported as 4.09 (95% CI, 1.61 to 10.41) for

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				pramipexole, 2.73 (95% CI, 1.01 to 7.39) for ropinirole and 6.22 (95% CI, 2.55 to 15.21) for cabergoline. There were no significant differences in the absolute risk reduction. The frequency of other adverse events including anxiety, depression, headache, dizziness/hypotension and nausea did not differ significantly among each of the dopamine agonists or compared to levodopa (*P*>0.1). Somnolence was only reported in trials comparing pramipexole or ropinirole to levodopa and occurred more often with pramipexole (*P*=0.032 vs levodopa) but not with ropinirole relative to levodopa (*P*=0.175). Secondary: Not reported
Whone et al[15] Ropinirole 0.25 mg TID increased to a maxium of 24 mg/day as needed vs carbidopa/levodopa 12.5/50 mg aily increased to a maximum of 1,000 mg of levodopa as needed Supplemental levodopa was prescribed as needed. Fixed dose amantadine and anticholinergic antiparkinson medications were	DB, MC, PRO, R Patients 30 to 75 years of age with ^{18}F-dopa PET evidence and a clinical diagnosis of Parkinson's disease, experiencing symptoms for ≤2 years	N=162 2 years	Primary: Change in putamen ^{18}F-dopa uptake (Ki) (a useful marker of disease progression) from baseline Secondary: Change from baseline in USDRS motor scores, proportion of patients scoring 1 (very much improved) or 2 (much improved) on the CGI global improvement scale over 1 year, incidence and time to development of dyskinesias	Primary: A significantly greater reduction in putamen Ki was observed with levodopa treatment (-20.30% [SE, 2.35]) relative to ropinirole therapy (-13.40% [SE, 2.14]); 95% CI, 0.65 to 13.06; *P*=0.022). Secondary: Ropinirole therapy was associated with an increase in the UPDRS motor score (0.70 points; SE, 0.97), while levodopa demonstrated a reduction in the score (-5.64 points; SE, 1.05) and therefore an improvement in symptoms. The difference in the change in motor function between levodopa and ropinirole was significant (95% CI, 3.54 to 9.14). The percentage of patients reporting either a 1 or a 2 on the CGI global improvement scale was comparable between groups (67.80% for ropinirole vs 74.70% for levodopa; OR, 0.72; 95% CI, 0.36 to 1.45; *P*=0.367). There was a significant reduction in the risk of developing dyskinesias with ropinirole (3.40%) relative to levodopa (26.70%; OR, 0.09; 95% CI, 0.02 to 0.29; *P*<0.001). The difference in time to development of dyskinesias was significant and also favored ropinirole (*P*<0.001). Supplemental levodopa was required in 15 (17.0%) patients in the ropinirole group and 7 (9.0%) in the levodopa group. The most common adverse drug reactions

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permitted.				noted were nausea and somnolence and both were more often associated with ropinirole use (43.7% and 37.9% respectively vs 21.3% and 9.3% for levodopa).
Stowe et al[16] Dopamine agonists with or without levodopa vs levodopa or dopamine agonists with or without levodopa vs placebo or dopamine agonists with or without levodopa vs levodopa and placebo	MA Patients of any age with early idiopathic Parkinson's disease, no history of motor complications, either untreated or with limited exposure to anti-parkinsonian medications	N=5,247 (29 trials) 8 weeks – 10 years	Primary: Symptom control, motor complications, side effects, withdrawals Secondary: Not reported	Primary: Levodopa was reported to be of benefit over dopamine agonists in overall symptom control, although there was insufficient data available to meta-analyze results. Freezing was more often with dopamine agonist therapy vs levodopa (OR, 1.58; 95% CI, 1.14 to 2.18; *P*=0.005), but this outcome was only reported in 5 trials. Compared to placebo, dopamine agonist therapy was associated with significant improvements in symptom control. The risk of developing motor complications was reduced in patients receiving agonist therapy compared to levodopa, including dyskinesia (OR, 0.51; 95% CI, 0.43 to 0.59; *P*<0.00001), dystonia (OR, 0.64; 95% CI, 0.51 to 0.81; *P*=0.0002) and motor fluctuations (OR, 0.75; 95% CI, 0.63 to 0.90; *P*=0.002). Conversely, there was an increased risk of developing non-motor side effects associated with dopamine agonist use vs levodopa. Edema (OR, 3.68; 95% CI, 2.62 to 5.18; *P*<0.00001), somnolence (OR, 1.49; 95% CI, 1.12 to 2.00; *P*=0.007), constipation (OR, 1.59; 95% CI, 1.11 to 2.28; *P*=0.01), dizziness (OR, 1.45; 95% CI, 1.09 to 1.92; *P*=0.01), hallucinations (OR, 1.69; 95% CI, 1.13 to 2.52; *P*=0.01) and nausea (OR, 1.32; 95% CI, 1.05 to 1.66; *P*=0.02) were all more frequently reported in patients taking dopamine agonists than with levodopa. Subsequently, a greater number of patient in the dopamine agonist group discontinued treatment secondary to side effects (OR, 2.49; 95% CI, 2.08 to 2.98; *P*<0.00001). Analysis between individual agonists was reported in regards to reduction in dyskinesia. There was a 59% decrease in dyskinesia for both cabergoline and pergolide, 71% for both pramipexole and ropinirole and 35% decrease with bromocriptine (*P*=0.008). Secondary: Not reported

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Fung et al[17] Levodopa/carbidopa and entacapone administered as separate entities vs levodopa/carbidopa Patients discontinued their commercial levodopa/ carbidopa preparation and commenced their blinded study drug at equivalent doses of levodopa/ carbidopa, with or without entacapone, on the day after baseline visit. Mean levodopa dose at baseline in the levodopa/ carbidopa and entacapone group was 395.2 mg and 420.0 mg for the levodopa/ carbidopa group.	AC, DB, MC, RCT Patients ≥30 years old with idiopathic Parkinson's disease, a modified Hoehn & Yahr stage of 1.0-2.5, and 0.0-3.0 hours of nondisabling off-time over a consecutive 48 hour period, were required to be taking 3-4 stable equal doses of levodopa/carbidopa with a total daily levodopa dose of 300-800 mg/day for at least 1 month before study entry	N=184 12 weeks	Primary: Change from baseline to week 12 in the total PDQ-8 score Secondary: Change from baseline to week 4 and week 12 in: UPDRS parts I,II,III and IV subscale scores, UPDRS parts I-III combined, number of wearing-off symptoms, proportion of patients experiencing wearing-off using the Wearing-Off Card and safety	Primary: The levodopa/carbidopa and entacapone treatment group had a mean improvement in their PDQ-8 scores of 0.8 point. The levodopa/carbidopa group had a mean deterioration in the PDQ-8 of 0.6 point. The 1.4 point difference between the two groups was found to be statistically significant (*P*=0.021). A subgroup analysis of the individual PDQ-8 questions showed that the treatment difference favored the levodopa/carbidopa and entacapone treatment group and was statistically significant in questions: • #3: Depression (*P*=0.025) • #4: Close personal relationships (*P*=0.037) • #6: Communication (*P*=0.007) • #8: Social stigma (*P*=0.033) Secondary: The mean UPDRS part II scores improved in the levodopa/ carbidopa and entacapone group but not in the levodopa/ carbidopa group. The difference was not statistically significant at week 4 (*P*=0.057) but did reach significance by week 12 (*P*=0.032). The difference in part III results between the two treatment groups did not achieve statistical significance (*P*=0.087). Parts I and IV had very low baseline scores and did not demonstrate a significant change over the 12 week treatment period (*P* values not reported). The combined UPDRS parts I-III scores improved in both treatment groups at week 4 and 12. However the difference between the two treatment groups did not reach significance at week 4 (*P*=0.071), but did at week 12 (*P*=0.047). The mean number of wearing-off symptoms across all patients at baseline was 4.4 and this was reduced to 3.1 at week 12. There was no significant difference in the reduction of wearing-off symptoms between the two groups (*P* values not reported). Patients in levodopa/carbidopa and entacapone treatment group who experienced at least one wearing-off symptom was 78.5% at baseline and decreased to 69.8% and 61.8% at weeks 4 and 12 respectively. Patients in the levodopa/carbidopa group had an 84.6% at baseline and this decreased to 61.5% at both weeks 4 and

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				weeks 12. There was no statistically significant difference between the two groups (*P* values not reported). Both of the treatment regimens were safe and well tolerated over the study period. Adverse events attributed to the discontinuation of the study in 14 patients (7.6%). In the levodopa/carbidopa and entacapone treatment group 66% of patients had at least one adverse event and this number was 56% in the levodopa and carbidopa group. The most common adverse events were: • Urine discoloration: (23% levodopa/carbidopa and entacapone vs 6% levodopa/carbidopa) • Nausea: (12% levodopa/carbidopa and entacapone vs 8% levodopa/carbidopa) • Dizziness: (5% levodopa/carbidopa and entacapone vs 7% levodopa/carbidopa) • Constipation: (5% levodopa/carbidopa and entacapone vs 3% levodopa/carbidopa) • Diarrhea: (5% levodopa/carbidopa and entacapone vs 4% levodopa/carbidopa)
Olanow et al[18] Levodopa/carbidopa and entacapone 200 mg administered as separate entities vs levodopa/carbidopa and placebo administered as separate entities Mean levodopa dose at baseline in the entacapone group was	DB, MC, PC, PG, RCT Patients were male or female ≥30 years older with idiopathic Parkinson's disease, had at least two of the following: rigidity, resting tremor, and bradykinesia; doses of levodopa had to be stable for one month prior to study	N=750 26 weeks	Primary: Change from baseline to week 26 in the motor subscale score of the UPDRS Secondary: Change from baseline to week 26 in: ADL subscale scores of the UPDRS, total UPDRS score, PDQ-39, SF-36, PSI, need for	Primary: Change from baseline in the motor subscale score of the UPDRS to week 26 was -0.9 for the entacapone group and -0.8 for the placebo group. This change was not statistically significant (*P*=0.83). Secondary: Changes from baseline in the ADL subscale score was -0.1 for the entacapone group and 0.2 for the placebo group. The difference between the two groups was not significant (*P*=0.16). Changes from baseline in the total UPDRS score was -0.9 for the entacapone group and -0.4 in the placebo group. The difference between the groups was not significant (*P*=0.42). Changes in the PDQ-39 scores were -0.7 in the entacapone group and 1.6 in the placebo group with the difference between these results reaching statistical significance (*P*<0.001).

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401 mg and 406 mg for the placebo group.	initiation		supplemental dopaminergic therapy and safety	Statistically significant differences in the SF-36 scores were seen for the subsections of:
				• Physical functioning (*P*=0.047):
				  ○ Entacapone Change Score: -0.1
				  ○ Placebo Change Score: -0.2
				• Vitality domain (*P*=0.04):
				  ○ Entacapone Change Score: -0.0
				  ○ Placebo Change Score: -0.1
				• Physical component (*P*=0.009):
				  ○ Entacapone Change Score: -0.6
				  ○ Placebo Change Score: -1.9
				
				Frequency and distress measures of the PSI test had significant improvements in the entacapone group
				• Frequency (*P*=0.007):
				  ○ Entacapone Change Score: -1.5
				  ○ Placebo Change Score: 0.2
				• Distress Change Score (*P*=0.02):
				  ○ Entacapone Change Score: -1.4
				  ○ Placebo Change Score: 0.3
				
				More patients in the placebo group (12.5%) required an increase in levodopa dose than did the entacapone group (8.0%; *P*=0.046*)*.
				
				Seven patients died during the course of the study. None of their deaths were attributed to the study medication. Nausea and dyskinesia were the most common observed adverse events. The rate of nausea was 18.2% in the entacapone group and 11.7% in the placebo group. For dyskinesia 12.6% in the entacapone group and 10.9% in the placebo group.

Boiko et al[19] Levodopa/DCI at a dose up to 750 mg/day administered as a	MC, OL Patients with idiopathic Parkinson's	N=50 6 weeks	Primary: Change from baseline at week 6 in UPDRS scores	Primary: By week 6, treatment with levodopa/carbidopa/ entacapone was shown to cause a 29.2% reduction in the overall UPDRS score. Subscale scores of the UPDRS indicated the following:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination product vs levodopa/carbidopa/ entacapone 200 mg administered as a combination product Dose determined according to patients daily levodopa dose taken prior to start of study.	disease with motor fluctuations (wearing-off of the effects of single levodopa dose, and experiencing on-off phenomenon)		Secondary: Safety	• A decrease in the UPDRS score of mental functions from 3.6 to 2.5 (*P*<0.0001). • Activities of daily living scores improved from a score of 14.3 to 10.7 (*P*<0.0001). • Motor impairments improved from a score of 24.2 to 19.4 (*P*<0.0001). • The complications of treatment score decrease from 4.0 to 3.3 (*P*<0.001). Secondary: Less than 10% of patients reported nausea, orthostatic reactions and headache. None of the adverse effects warranted corrective treatment.
Koller et al[20] Levodopa/carbidopa 25/100 mg (1/2 tablet, 1 tablet, 1 ½ tablet) administered as a combination product vs levodopa/carbidopa/ entacapone administered as a combination product Dose of combination levodopa/carbidopa/ entacapone based on patient's dose of levodopa/carbidopa prior to start of study.	MC, OL Male and female patients ≥30 years old with idiopathic Parkinson's disease and exhibiting at least two out of three symptoms (rigidity, resting tremor, bradykinesia) and who were experiencing wearing-off with or without mild dyskinesia	N=169 4 weeks	Primary: The percent of patients who discontinued the study due to adverse events Secondary: The percent of subjects experiencing new onset dyskinesia and worsening of pre-existing dyskinesia, change from baseline in the UPDRS (Parts II,III, and II&III), change from baseline in UPDRS question-39, change from baseline on the	Primary: Seven percent of patients in the study withdrew due to adverse events. Common adverse events listed were nausea, continued or worsening off-periods, dizziness and discoloration of the urine. Secondary: Of the entire patient population 8.5% of patients who did not have dyskinesia at the onset of the study developed it, and 43.6% experienced a worsening of their already existing dyskinesia symptoms. UPDRS scores improved significantly in all parts and their values were as follows: • Part II: 1.7 reduction from baseline (*P*<0.001) • Part III: 3.9 reduction from baseline (*P*<0.001) • Parts II & III: 5.6 reduction from baseline (*P*<0.001) • Question 39: 0.3 reduction from baseline (*P*<0.001) PDQ-39 scores also improved significantly with a reduction in baseline of 4.0 (*P*<0.001). Investigators and patients noted improvement in treatment. At the end of the study investigators noted some degree of improvement in 68.1% of patients. 68.6% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			PDQ-39 total score and investigators and patient clinical assessments	patients also reported improvements.
Brooks et al[21] Levodopa/carbidopa and entacapone 200 mg administered as separate entities vs levodopa/carbidopa/ entacapone 200 mg administered as a combination product Patients in the combination levodopa/carbidopa/ entacapone arm received an equal amount of levodopa that was used during the 2 week run-in period for 6 weeks.	AC, MC, OL, PG, RCT Male and female patients with a mean age of 65 with idiopathic Parkinson's disease, were required to have end-of-dose wearing-off for at least 1 year prior to study entry, as well as answered "Yes" to at least one question in the 7-point MFQ, all patients were also required to have Hoehn and Yahr staging of 1 to 3	N=177 10 weeks 2 week run-in period, 6 week treatment period, 2 week follow-up period	Primary: Treatment success rate assessed by the patient at week 6 as evaluated by the 7-point CGI-C Secondary: Treatment success rate assessed by the investigators at week 6 as evaluated by: 7-point CGI-C, change in MFQ scores from baseline, change in UPDRS Part III score from baseline and safety	Primary: At week 6, 73% of the patients in the combination product treatment group and 76% in the separate entity group indicated they were in better clinical condition (*P* values not reported). Secondary: According to the investigators 79% of patients in both the combination product treatment group and the separate entity group were in better clinical condition (*P* values not reported). At week 6 motor fluctuations were reduced from baseline falling from 100% of cases to 64% in the combination product group and 73% in the separate entity group (*P* values not reported). In the combination product group 87% of patients and 81% of the patients in the separate entity group reported improved responses on the MFQ (*P* values not reported). At week 6 the UPDRS scores were significantly improved from baseline in both the combination product group ($P<0.001$) and the separate entity group ($P=0.0016$). Adverse events were reported in 55% of the total patient population and resulted in 5% of the patients discontinuing from the study. The most common adverse events seen were nausea, diarrhea, dyskinesia, abnormal urine, dizziness, influenza-like symptoms, back pain and insomnia. There was no significant difference in the adverse events between the two treatment groups (*P* values not reported).

Drug regimen abbreviations: TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DCI=dopa decarboxylase inhibitor, MA=meta-analysis, MC=multicenter, OL=open labeled, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, SR=systemic review
Miscellaneous abbreviations: ADL=Activities of Daily Living, CGI=Clinical Global Impression, CGI-C=Clinical Global Impression of Change, MAO-B=monoamine oxidase-B, MFQ=Motor Fluctuation Questionnaire, PDQ-8=Parkinson's disease Questionnaire, PET=positron emission tomography, PSI=Parkinson's Symptom Inventory, SE=standard error, SF=short form, UPDRS=Unified Parkinson Disease Rating Scale

Special Populations

Table 5. Special Populations[2-6]

Generic Name	Population and Precaution					
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
Carbidopa/ levodopa	Safety and efficacy not established in pediatric patients. Use with caution in the elderly as they may be more sensitive to the central nervous system effects of levodopa.	Use with caution in patients with renal impairment.	Use with caution in patients with hepatic impairment.	C	Unknown	Use with caution in patients with cardio-vascular, respiratory and endocrine disease, wide-angle glaucoma and psychiatric disorders.

Adverse Drug Events

Patients receiving any formulation of carbidopa/levodopa may develop dyskinesias. Dyskinesias are a common side effect of carbidopa/levodopa treatment. The occurrence of dyskinesias may require dosage reduction.[2-6]

Table 6. Adverse Drug Events (%)[2-6]

Adverse Event	Carbidopa/levodopa (Sinemet®) (%) reported	Carbidopa/levodopa (Sinemet CR®) (%) reported	Carbidopa/levodopa (Parcopa®) (%) reported
Cardiovascular			
Orthostatic hypotension	1.1	1	✔
Central and Peripheral Nervous System			
Confusion	2.3	3.7	✔
Depression	1.3	2.2	✔
Dizziness	2.3	2.9	✔
Dream abnormalities	0.8	1.8	✔
Dyskinesia	12.2	16.5	✔
Dystonia	0.8	1.8	✔
Hallucination	3.2	3.9	✔
Headache	1.9	2.0	✔
Insomnia	1	1.2	✔
'On-Off' phenomena	1.1	1.6	✔
Paresthesia	1.1	0.8	✔
Gastrointestinal			
Anorexia	1.1	1.2	✔
Constipation	1.5	0.2	✔
Diarrhea	0.6	1.2	✔
Dry mouth	1.1	1.4	✔
Dyspepsia	1.1	0.6	✔
Nausea	5.7	5.5	✔
Vomiting	1.9	1.8	✔

Adverse Event	Carbidopa/levodopa (Sinemet®) (%) reported	Carbidopa/levodopa (Sinemet CR®) (%) reported	Carbidopa/levodopa (Parcopa®) (%) reported
Respiratory			
Dyspnea	0.4	1.6	✔
Upper respiratory infection	1	1.8	✔
Urinary System			
Urinary frequency	1.1	0.8	✔
Urinary tract infection	2.3	2.2	✔
Other			
Back pain	0.6	1.6	✔
Chest pain	0.8	1	✔
Shoulder pain	0.6	1	✔

✔ Percent not reported.

Contraindications / Precautions[2-6]

Carbidopa/levodopa is contraindicated in patients with hypersensitivity to any components of the drug.

Nonselective monoamine oxidase inhibitors (MAO) are contraindicated for use in patients on carbidopa/levodopa therapy. These inhibitors must be discontinued two weeks prior to the initiation of therapy with carbidopa/levodopa. The use of MAO inhibitors with selectivity for MAO type B is acceptable and may be appropriate for some patients. Carbidopa/levodopa is also contraindicated in patients with narrow-angle glaucoma and in patients with a history of melanoma/undiagnosed skin lesions.

Drug Interactions

Table 7. Drug Interactions[2-6]

Drug Name	Interacting Medication or Disease	Potential Result
Dopamine precursor/ dopa decarboxylase inhibitors	Antihypertensive agents	Systemic postural hypotension may occur; dosage adjustment of the antihypertensive drug may be required.
Dopamine precursor/ dopa decarboxylase inhibitors	Dopamine-D_2 receptor antagonists	Reduction in therapeutic effects of levodopa. Effects of levodopa in Parkinson's disease may be reversed. Patients should be monitored for loss of therapeutic response.
Dopamine precursor/ dopa decarboxylase inhibitors	Monoamine oxidase-B (MAO-B) inhibitors	Severe orthostatic hypotension may occur.
Dopamine precursor/ dopa decarboxylase inhibitors	Metoclopramide	Concurrent administration may increase bioavailability of levodopa by increasing gastric emptying. May also adversely affect disease control by its dopamine receptor antagonistic properties.
Dopamine precursor/ dopa decarboxylase inhibitors	Tricyclic antidepressants	Patients may experience hypertension and dyskinesia.

Dosage and Administration

Table 8. Dosing and Administration[2-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Carbidopa/ levodopa	Idiopathic Parkinson's disease, postencephalitic parkinsonism, symptomatic parkinsonism: Controlled-release tablet: initial, one tablet twice daily at an interval of every 6 hours; maintenance, individualize, minimum of 70-100 mg of carbidopa to minimize nausea and vomiting; maximum, 200 mg of carbidopa Tablet: initial, 10/100 or 25/100 as one tablet three times a day; maintenance, individualize, minimum of 70-100 mg of carbidopa to minimize nausea and vomiting; maximum, carbidopa 200 mg Orally disintegrating tablet: initial, 10/100 or 25/100 as one tablet three times a day; maintenance, individualize, minimum of 70-100 mg of carbidopa to minimize nausea and vomiting; maximum, 200 mg carbidopa	Safety and efficacy in children have not been established.	Controlled-release tablet: 25/100 mg 50/200 mg Orally disintegrating tablet: 10/100 mg 25/100 mg 25/250 mg Tablet: 10/100 mg 25/100 mg 25/250 mg

Clinical Guidelines

According to the National Institute for Health and Clinical Excellence (NICE) there is no universal first-choice therapy for patients with Parkinson's disease.[7] Levodopa, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors may all be used in patients with early Parkinson's disease for symptomatic treatment. The MAO-B inhibitors are considered more convenient compared to the other agents due to ease of administration and may be considered in patients who need symptomatic treatment prior to the administration of dopaminergic therapy. Anticholinergics should be limited to younger patients with early Parkinson's disease associated with severe tremor. In elderly patients, early use of levodopa is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events.

In addition, there is no single agent of choice for late stage Parkinson's disease.[7] Levodopa, dopamine agonists, MAO-B inhibitors and catechol-O-methyl transferase (COMT) inhibitors may all be considered to reduce motor fluctuations in patients with late stage Parkinson's disease. For the symptomatic control of wearing-off in late, complicated Parkinson's disease, several strategies have been recommended. Such strategies include increasing the dosing frequency of levodopa or switching to a controlled-release formulation of the medication. Also adding a COMT-inhibitor, MAO-B inhibitor or dopamine agonist as adjunctive therapy is also recommended. If these strategies fail it is recommended that amantadine or an anticholinergic be considered. For the symptomatic control of dyskinesias in late, complicated Parkinson's disease the addition of amantadine is recommended. Other strategies include reducing the dose size of levodopa or discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors, however these strategies increase the risk of worsening off-time.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
National Institute for Health and Clinical Excellence (NICE): **Parkinson's Disease: Diagnosis and**	• There is no universal first-choice therapy for patients with Parkinson disease (PD). Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early PD for symptomatic treatment with doses kept as low as possible to reduce the

Clinical Guideline	Recommendations
Management in Primary and Secondary Care (2006)[7]	development of motor complications. • Dopamine agonists may be used in patients with early PD for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if the patient fails therapy or side effects prevents titration. • Monoamine oxidase-B (MAO-B) inhibitors may be used in patients with early PD for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early PD, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early PD for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric side effects. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early PD. • Most patients with PD will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage PD. • There is no single agent of choice for late stage PD. • Extended-release levodopa may help reduce motor complications in patients with late stage PD, but is not considered a first-line agent. • Dopamine agonists may be used to reduce motor fluctuations in patients with late stage PD. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if side effects prevent titration. • MAO-B inhibitors may be used to reduce motor fluctuations in patients with late stage PD. • Catechol-O-methyl transferase (COMT) inhibitors may be used to reduce motor fluctuations in patients with late stage PD. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage PD. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.
American Academy of Neurology (AAN) Practice Parameter: **Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)[8]**	• Patients with PD, who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in PD, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living (ADL) in patients with PD who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor complications and ADL disability and is associated with a higher incidence of dyskinesias than dopamine agonists. • Levodopa or a dopamine agonist may be initiated in patients with PD who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (i.e., wearing off, dyskinesias, on-off fluctuations)

Clinical Guideline	Recommendations
	compared to levodopa. • Treatment with a dopamine agonist was associated with more frequent adverse drug reactions (hallucinations, somnolence and edema in the lower extremities) than levodopa. • When initiating treatment with levodopa in patients with PD, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
AAN Practice Parameter: **Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)**[9]	• Rasagiline and entacapone demonstrated statistically significant reduction in off time as compared to placebo in clinical trials. It is recommended that these two agents should be offered to reduce off-time. • Pergolide demonstrated some improvement in the reduction in off-time as compared to placebo in clinical trials. However, a large number of patients on pergolide experienced more dyskinesias. Pramipexole demonstrated some reduction in off-time in placebo controlled trials. Ropinirole and tolcapone showed reduction in off-time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce off-time. Due to side effects and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing off-time. It is recommended that these agents may be considered to reduce off-time. • Bromocriptine and extended-release carbidopa/levodopa do not help to reduce off-time. • Amantadine demonstrated reduction in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with PD for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in PD patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Early (Uncomplicated) Parkinson's Disease (2006)**[10]	• No adequate clinical trials have been conducted to provide definitive evidence for pharmacological neuroprotection. • In the management of early PD, MAO-B inhibitors have a modest benefit in treating the symptomatic complications of PD compared to levodopa and dopamine agonists. These agents are more convenient due to the ease of administration (i.e., one dose, once daily, no titration). • Amantadine and anticholinergics offer minimal symptom control compared to levodopa. • Anticholinergics are poorly tolerated in the elderly and use should be restricted to younger patients. • Levodopa is the most effective anti-Parkinson's drug for symptomatic relief. • Early use of levodopa in the elderly is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events. • Pramipexole and ropinirole are effective dopamine agonists as monotherapy in the treatment of early stage PD. • Convincing evidence that older agents in the class are less effective

Clinical Guideline	Recommendations
	than the newer non-ergot agents is lacking. • Dopamine agonists have a lower risk of developing motor complications than compared to levodopa. These agents do have a greater incidence of adverse effects which include hallucinations, somnolence and edema in the lower extremities. • Younger patients should be started on a dopamine agonist as initial treatment to prolong the use of levodopa and the development of motor complications.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Late (Complicated) Parkinson's Disease (2006)**[11]	Symptomatic Control of Wearing-off • Adjusting the levodopa dose by increasing the dosing frequency has been beneficial to control off-time. • Switching from the standard formulation of levodopa to the controlled-release formulation improves wearing-off symptoms. • Adding a COMT-inhibitor or a MAO-B inhibitor is effective in reducing off-time by 1-1.5 hours/day. • Adding a dopamine agonist provides modest benefit. All dopamine agonists are equally effective and efficacious in reducing off-time. Pergolide and other ergot derivatives are reserved for second-line use, due to the adverse effect of valvulopathy. • Addition of amantadine or anticholinergics should be considered in patients with severe off symptoms who fail the recommended strategies listed above. Symptomatic Control of Dyskinesias • Patients may benefit for up to 8 months by adding amantadine 200-400 mg/day for the treatment of dyskinesias. • Reducing the dose size of levodopa has been beneficial in reducing dyskinesias. The risk of off-time increases but can be compensated by increasing the frequency of levodopa dosing. • Discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors can help control dyskinesias, however the risk of worsening off-time increases. • The addition of clozapine or quetiapine has shown to be beneficial in reducing peak dose dyskinesia. Clozapine's adverse effect of agranulocytosis limits its use. • Deep brain stimulation of the subthalamic nucleus allows the reduction of dopaminergic treatment. • Apomorphine given as a continuous subcutaneous infusion under direct medical supervision allows for the reduction of levodopa therapy and helps control dyskinesias.

Conclusions

Parkinsonian syndrome is related to the depletion of dopamine in the corpus striatum. Levodopa is the metabolic precursor of dopamine that crosses the blood-brain barrier, and works by presumably increasing dopamine concentrations in the brain.[1-5] Formulations are currently available in combination with carbidopa, a peripheral decarboxylase inhibitor, which helps prevent the peripheral metabolism of levodopa to dopamine. Carbidopa also helps to prevent nausea and vomiting associated with circulating dopamine.

Parkinson's disease is incurable, but may be managed properly for a number of years. Medications to slow the progression of disease or provide neurological protection are yet to be discovered. When Parkinson's disease symptoms become moderate to severe, it often affects the patient's quality of life and activities of daily living resulting in the need for daily assistance. Most patients will eventually need

levodopa therapy to treat the symptomatic motor complications associated with Parkinson's disease. However, long-term levodopa use is associated with side effects, such as dyskinesia and dystonia. Doses of levodopa should be initiated at the lowest most effective dose to help delay the development of motor complications. Prolonged levodopa use is also associated with the on-off phenomena. This can be managed by changing to the controlled-release formulation or adding a dopamine agonist, catechol-O-methyl transferase (COMT) inhibitors or monoamine oxidase-B (MAO-B) inhibitors.[7-11] An overview of the currently available Parkinson's disease guidelines indicates that there is no overall agreement between the guidelines as to which is the preferred agent for initial treatment. However the guidelines are in agreement that levodopa produces the most efficacious relief of Parkinson's symptoms.[7-11]

Recommendations

In recognition of the well-established role of the dopamine precursor/dopa decarboxylase inhibitors for the treatment of Parkinson's disease, and the lack of well-documented clinically significant differences in efficacy amongst the products, no changes are recommended to the current approval criteria.

Generic carbidopa/levodopa products are preferred on The Office of Vermont Health Access (OVHA) preferred drug list. The brands require prior authorization with the following approval criteria:

- The patient has had a documented intolerance to the generic product.

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